Please amend claim 44, as follows:

24 ~~44~~. **(Amended)** A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any one of claims 1-23, and a pharmaceutical acceptable carrier.

Please add new claim 65, as follows:

25 ~~65~~. The pharmaceutical composition of claim ~~44~~ 24, which further comprises at least one additional therapeutic agent.--

REMARKS

Claims 1-64 were pending in the application. Claims 24-43 and 47-64, directed to non-elected inventions, have been canceled without prejudice to further prosecution in a divisional application(s). Claims 45 and 46, directed to pharmaceutical compositions, have also been canceled and claim 44, also directed to a pharmaceutical composition, has been amended to be in multidependent claim format. Support for the amendment to claim 44 can be found in the claims as originally filed and in the specification at, for example, page 23-25. New claim 65, directed to a pharmaceutical composition including an antibody of the invention and at least one additional therapeutic agent, has been added. Support for new claim 65 can be found in the specification at, for example, page 25, lines 3-16 and pages 28-31. Accordingly, claims 1-23, 44 and 65 are currently pending.

For the Examiner's convenience, a copy of the claims as currently pending after the amendments herein is provided as Appendix A.

Objection to Specification and Rejection of Claims 1 and 3 under 35 U.S.C. §112, First Paragraph

The specification was objected to and claims 1 and 3 were rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure. In particular, the Examiner argues that "the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) can be reproducibly isolated; or (3) deposited." The Examiner further states that "[i]t unclear if a cell line which produces an antibody having the exact structural and chemical identity of D2E7 is known and publicly available, or can be reproducibly isolated without undue experimentation" and that "[e]xact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event." Applicants respectfully traverse this rejection.

First, Applicants note that none of the claims are directed to "a cell line which produces an antibody having the exact structural and chemical identity of D2E7." Claims 1 and 3 are directed to human antibodies that bind to human TNFα and have other recited characteristics, of which D2E7 is only one example. The specification provides many other examples of antibodies that meet the limitations recited in claims 1 and 3.

Furthermore, it is Applicants' position that the ordinarily skilled artisan can reproduce an antibody having the claimed binding characteristics, including the precise antigen-binding characteristics of the D2E7 antibody, in view of the instant disclosure. More particularly, the specification discloses the full amino acid sequences of the light and heavy chain variable regions for the D2E7 antibody (shown in SEQ ID NOs: 1 and 2, respectively, and Figures 7 and 8, respectively) and the nucleotide sequences encoding these light and heavy chain variable regions (shown in SEQ ID NOs: 36 and 37,

respectively, and Figures 7 and 8, respectively). The specification still further provides the amino acid sequences of the light and heavy chain variable regions for many other antibody of the invention (see Figures 1 and 2 and SEQ ID NOs: 3-35), including delineating the complementarity determining regions (CDRs) thereof It is well known in the art that the antigen-binding properties of an antibody are conferred by its variable regions and in particular by the CDRs. The amino acid sequences for human antibody constant regions are readily available in the art. The specification also described in detail how to make antibodies having the recited characteristics using the nucleotide and/or amino acid sequences provided in the specification and standard recombinant molecular biology techniques (see *e.g.*, page 15, line 29 through page 20, line 9).

In view of these disclosures, it is Applicants' position that the specification adequately described and enables the claimed antibodies. Accordingly, Applicants request that this objection to the specification and rejection of claims 1 and 3 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn. If the Examiner insists on maintaining this rejection, Applicants request that the Examiner provide specific reasons why one of ordinary skill in the art could not reproduce an antibody having the antigen-binding properties of the D2E7 antibody in view of the disclosure within the specification of the amino acid and nucleotide sequences of the V_L and V_H regions of D2E7 and the guidance provided regarding how to recombinantly express the antibodies of the invention.

Rejection of Claims 1-23 and 44-46 under 35 U.S.C. §112, First Paragraph

Claims 1-23 and 44-46 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. In support of this rejection, the Examiner states that

> [t]he specification fails to provide any teachings as to how one skilled in the art is to obtain human antibodies having the recited characteristics. As an example, there is no teaching as to the origin of the D2E7 antibody or how this antibody was obtained. Absent such teaching, one skilled in the art has no means by which to obtain antibodies within the scope of the claims since the manner with which such antibodies are to be isolated is not taught. There is no teaching as to where and/or how one skilled in the art is to make antibodies having the recited characteristics. The specification teaches that naturally occurring human antibodies, generally, have low binding affinities for human TNF-α, see specification, page 2, lines 7-34. Thus, one skilled in the art would be subjected to undue experimentation in order to practice the invention as currently claimed.

Applicants respectfully traverse this rejection.

Contrary to the Examiner's assertions, the specification provides extensive teachings and guidance regarding the origin of the D2E7 antibody and how to make other antibodies having the recited characteristics. For example, the specification describes, as a preferred embodiment, the preparation of human anti-hTNFα antibodies starting from a mouse anti-hTNFα monoclonal antibody (preferably MAK 195, a publicly deposited hybridoma) using the "epitope imprinting method", which is how the D2E7 antibody originated. More specifically, the specification states (at page 22, lines 25-34) that

> [i]n a preferred embodiment, to isolate human antibodies with high affinity and a low off rate constant for hTNFα, a murine anti-hTNFα antibody having high affinity and a low off rate constant for hTNFα (*e.g.*, MAK 195, the hybridoma for which has deposit number ECACC 87 050801) is first used to select human heavy and light chain sequences having similar binding activity toward hTNFα, using the epitope imprinting methods described in Hoogenboom *et al.*, PCT Publication No. WO 93/06213. The antibody libraries used in this method are preferably scFv libraries prepared and screened as described in McCafferty *et al.*, PCT Publication No. WO 92/01047, McCafferty *et al.*, *Nature* (1990) 348:552-554; and

> Griffiths *et al.*, (1993) *EMBO J* 12:725-734. The scFv antibody libraries preferably are screened using recombinant human TNFα as the antigen.

The specification goes on to describe how to improve the binding properties of the initially selected antibodies. For example, the specification states (at page 22, line 35 through page 23, line 9) that

> [o]nce initial human VL and VH segments are selected, "mix and match" experiments, in which different pairs of the initially selected VL and VH segments are screened for hTNFα binding, are performed to select preferred VL/VH pair combinations. Additionally, to further improve the affinity and/or lower the off rate constant for hTNFα binding, the VL and VH segments of the preferred VL/VH pair(s) can be randomly mutated, preferably within the CDR3 region of VH and/or VL, in a process analogous to the *in vivo* somatic mutation process responsible for affinity maturation of antibodies during a natural immune response. This *in vitro* affinity maturation can be accomplished by amplifying VH and VL regions using PCR primers complimentary to the VH CDR3 or VL CDR3, respectively, which primers have been "spiked" with a random mixture of the four nucleotide bases at certain positions such that the resultant PCR products encode VH and VL segments into which random mutations have been introduced into the VH and/or VL CDR3 regions. These randomly mutated VH and VL segments can be rescreened for binding to hTNFα and sequences that exhibit high affinity and a low off rate for hTNFα binding can be selected.

The specification still further describes how to recover, express and manipulate antibodies of interest. For example, the specification states (at page 23, lines 10-18) that

> [f]ollowing screening and isolation of an anti-hTNFα antibody of the invention from a recombinant immunoglobulin display library, nucleic acid encoding the selected antibody can be recovered from the display package (*e.g.*, from the phage genome) and subcloned into other expression vectors by standard recombinant DNA techniques. If desired, the nucleic acid can be further manipulated to create other antibody forms of the invention (*e.g.*, linked to nucleic acid encoding additional immunoglobulin domains, such as additional constant regions). To express a recombinant human antibody isolated by screening of a

> combinatorial library, the DNA encoding the antibody is cloned into a recombinant expression vector and introduced into a mammalian host cells, as described in further detail in Section II above.

The specification also provides citations for additional combinatorial screening approaches that can be used to isolate additional antibodies of the invention (see page 22, lines 5-24). With regard to the details of the particular methodologies taught by these cited publications, and the publications cited in the above-quoted passages, it is a well accepted principle that a patent need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). Moreover, each of these publications has been incorporated by reference into the instant specification (see page 31, lines 26-27).

In addition to the foregoing teachings regarding how to make antibodies of the invention starting from a mouse anti-hTNFα antibody or recombinant antibody libraries, the specification also describes how antibodies of the invention can be made using the amino acid and nucleotide sequences disclosed in the instant specification. For example, the specification describes (at page 16, lines 14-33) how to obtain DNA sequences encoding the V_L and V_H regions of the D2E7 antibody starting from germline human V_L and V_H sequences:

> To obtain a DNA fragment encoding the heavy chain variable region of D2E7, or a D2E7-related antibody, a member of the V_H3 family of human germline VH genes is amplified by standard PCR. Most preferably, the DP-31 VH germline sequence is amplified. To obtain a DNA fragment encoding the light chain variable region of D2E7, or a D2E7-related antibody, a member of the V_KI family of human germline VL genes is amplified by standard PCR. Most preferably, the A20 VL germline sequence is amplified. PCR primers suitable for use in amplifying the DP-31 germline VH and A20 germline VL sequences can be designed based on the nucleotide sequences disclosed in the references cited *supra*, using standard methods.
>
> Once the germline VH and VL fragments are obtained, these sequences can be mutated to encode the D2E7 or D2E7-related amino acid

> sequences disclosed herein. The amino acid sequences encoded by the germline VH and VL DNA sequences are first compared to the D2E7 or D2E7-related VH and VL amino acid sequences [shown in SEQ ID NOs: 1 and 2] to identify amino acid residues in the D2E7 or D2E7-related sequence that differ from germline. Then, the appropriate nucleotides of the germline DNA sequences are mutated such that the mutated germline sequence encodes the D2E7 or D2E7-related amino acid sequence, using the genetic code to determine which nucleotide changes should be made. Mutagenesis of the germline sequences is carried out by standard methods, such as PCR-mediated mutagenesis (in which the mutated nucleotides are incorporated into the PCR primers such that the PCR product contains the mutations) or site-directed mutagenesis.

The specification goes on to describe how the VH and VL segments can be manipulated, using standard recombinant DNA techniques, to prepare full-length antibody genes, Fab fragments and single chain antibodies (scFv antibodies) (see page 16, line 34 through page 17, line 29).

Still further, the specification describes mutagenesis studies of the D2E7 antibody of the invention that delineate the amenability of various amino acid residues to substitution, thereby providing antibodies related to D2E7, but differing in amino acid sequence from D2E7, that retain the desired binding properties (see *e.g.*, page 12, line 12 through page 13, line 7 and Examples 2 and 3). Example 3 of the application further provides additional D2E7-related antibodies (the V_L and V_H amino acid sequences of which are shown in Figures 1 and 2 and in the Sequence Listing).

With regard to the Examiner's statement that "[t]he specification teaches that naturally occurring human antibodies, generally, have low binding affinities for human TNF-α", Applicants note that these prior art antibodies discussed in the background section were prepared by different methods than those described in the specification for the antibodies of the invention. For example, antibodies prepared by Boyle *et al.* (discussed at page 2, lines 10-21) were prepared by the human hybridoma technique. The antibodies prepared by Griffiths *et al.* (discussed at page 2, lines 22-30) were prepared

recombinantly by screening phage display libraries expressing antibodies from unimmuzed humans but, importantly, the methods used by Griffiths *et al.* did not include any of the techniques taught by the instant specification for improving antibody affinity, such as the "epitope imprinting" method described in the instant application at page 22, lines 25-34 nor the methods for optimizing antibody affinity described at page 22, line 35 through page 23, line 9 of the instant application.

In view of the foregoing, the specification fully describes the subject matter of the claimed invention and enables the ordinarily skilled artisan to make and use the claimed subject matter without undue experimentation. Accordingly, Applicants respectfully requests that this rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Rejection of Claims 1-23 and 44-46 under 35 U.S.C. §103(a)

Claims 1-23 and 44-46 were rejected under 35 U.S.C. §103(a) as being unpatentable over Griffiths *et al.* (EMBO J.) in view of Lewis *et al.* (WO 95/23813) or Lewis *et al.* (J. Cell. Biochem.). The Examiner relies on Griffiths *et al.* for teaching "human antibodies to TNF-α derived from phage display libraries." The Examiner notes that "[t]he reference differs from the claimed invention in that the binding affinities and kinetics of antigen binding differ from those of the claimed human monoclonal antibodies." The Examiner relies on both Lewis references for teaching "the use of alanine scanning mutagenesis to increase the binding affinities and improve the kinetics of antigen binding of monoclonal antibodies." The Examiner argues that

> [o]ne of ordinary skill in the art at the time the invention was made would have been motivated to utilize alanine scanning mutagenesis to produce and select human TNF-α specific monoclonal antibodies having high binding affinities, slow dissociation constants, and improved antigen kinetics because such antibodies would have been useful for the production of diagnostic and therapeutic antibodies. From the teachings of

> the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants respectfully traverse this rejection.

The Examiner states that the binding affinities and kinetics of antigen binding of Griffith *et al.*'s antibodies "differ" from those of the claimed antibodies. More accurately, the binding affinities and kinetics of antigen binding of the instantly claimed antibodies are significantly better than those of Griffith *et al.*'s antibodies. It is well established that a *prima facie* case of obviousness is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Papesch*, 315 F.2d 381 (CCPA 1963). While in no way conceding that the Examiner has successfully established a *prima facie* case of obviousness for any of the claims, the superior properties of the claimed antibodies demonstrate their nonobviousness over Griffith *et al.*, alone or in combination with either of the Lewis references, for reasons discussed in further detail below.

Griffiths *et al.* report a K_{off} of 1.4×10^{-2} s^{-1} and a K_d of 6.4×10^{-6} M (as determined by surface plasmon resonance) for their human anti-hTNF antibodies (see Table IV at page 731). The antibodies of claim 1, and dependent claims thereof, exhibit a K_d of 1×10^{-8} M or less, representing approximately a 640-fold greater antigen affinity. The invention provides antibodies with even greater affinity than this (see *e.g.*, the table at page 10, which reports that the D2E7 antibody has a K_d of 2.6×10^{-10} M, representing approximately a 24,615-fold greater antigen affinity). The antibodies of claim 1 and 9 recite a K_{off} of 1×10^{-3} s^{-1} or less, the antibodies of claims 2 and 10 recite a K_{off} of 5×10^{-4} s^{-1} or less and the antibodies of claims 3 and 11 recite a K_{off} of 1×10^{-4} s^{-1} or less. These kinetics represent approximately a 14-fold, a 28-fold and a 120-fold slower off

rate, respectively, than the antibodies of Griffiths *et al.* The invention provides numerous antibodies having K_{off} rates less than 1 x 10^{-3} s^{-1} (see *e.g.*, Tables 2 and 3, which list 23 antibodies having K_{off} rates between about 8 x 10^{-4} s^{-1} and 2 x 10^{-5} s^{-1}). The D2E7 antibody of the invention has an average K_{off} rate of 4.38 x 10^{-5} s^{-1} (see Table 1), representing approximately a 320-fold slower off rate than the antibodies of Griffiths *et al.*

The Examiner argues that "improvements in antigen binding as high as eleven fold have been observed by Lewis *et al.*" and that "Lewis *et al.* also noted ten-fold slower antigen dissociation rates [*sic*]." However, as detailed above, the claimed antibodies of the invention have significantly better improvements in antigen binding properties and kinetics of antigen binding than those observed by Lewis *et al.* Accordingly, the antibodies of the invention have unexpectedly superior properties compared to the prior art and, therefore, are nonobvious over the prior art.

In addition to the foregoing, certain of the claimed antibodies comprise structural features that are neither taught or suggested by the prior art such that no *prima facie* case of obviousness has been established for these claimed antibodies. For example, claims 9, 12 and dependent claims thereof comprise a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or (for claim 9 and dependent claims thereof) by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9. Claims 9, 12 and dependent claims thereof also comprise a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or (for claim 9 and dependent claims thereof) by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12. Claims 13 and 14 further recite the presence of the CDR2 domains of SEQ ID NOs: 5 and 6 and the CDR1 domains of SEQ ID NOs:

7 and 8, respectively. Claim 15 and dependent claims thereof comprise a light chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 (which include the CDR3 domains of SEQ ID NOs: 3 and 4, the CDR2 domains of SEQ ID NOs: 5 and 6 and the CDR1 domains of SEQ ID NOs: 7 and 8). Claim 20 recites that the antibody comprises a light chain CDR3 and a heavy chain CDR3 selected from a group of specific amino acid sequences listed in the Sequence Listing. None of these structural features of the antibodies of claims 9-20 are taught or suggested by the prior art, as discussed further below.

For purposes of illustration, Applicants refer the Examiner to Appendix B, which compares the light chain CDR3 of SEQ ID NO: 3 and the heavy chain CDR3 of SEQ ID NO: 4 with the corresponding regions of the four anti-TNF antibodies disclosed in Table II of Griffiths *et al.* (at page 728). The amino acid residues underlined and in bold for SEQ ID NOs: 3 and 4 represent amino acid residues which differ from the corresponding positions in any of the four antibodies disclosed in Griffiths *et al.* Similarly, there are differences between the amino acid sequences of the CDR1 and CDR2 regions of Griffith *et al.*'s antibodies and those presented in SEQ ID NOs: 5-8. Furthermore, there are also differences between the amino acid sequences of the CDR3 regions of Griffith *et al.*'s antibodies and those presented in the SEQ ID NOs. listed in claim 20.

Regarding the obviousness of chemical compounds having defined structural features, the Court of Appeals for the Federal Circuit has stated that "[when] the prior art teaches a specific, structurally-definable compound . . .the question becomes whether the prior art would have suggested making the ***specific molecular modifications necessary to achieve the claimed invention***." *In re Deuel*, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995) (citing *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990), *et al.*) (emphasis

added). The CAFC further cited to *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) for the proposition that "[t]he prior art must provide one of ordinary skill in the art the motivation to make the ***proposed molecular modifications needed to arrive at the claimed compound***." *In re Deue*l, *Id.* at 1215 (emphasis added).

Neither the Griffiths *et al.* reference itself, nor the secondary references cited by the Examiner (the two Lewis references), provide the requisite suggestion or motivation to make the specific molecular modifications that would be necessary to arrive at the antibodies claimed in claims 9-20. The Examiner has not pointed to any teachings of the cited references that would suggest the specific structural features of the antibodies of claims 9-20, but has merely cited a method (disclosed in the Lewis *et al.* references) that the Examiner argues could be used to arrive at the claimed antibodies.

The CAFC, however, has rejected this rationale in attempting to establish a *prima facie* case of obviousness for claims to defined chemical compounds. In *In re Deuel*, cited *supra*, in which the PTO attempted to establish the obviousness of a defined DNA molecule by reliance on a prior art method for isolating DNA molecules, the CAFC stated that "[t]he PTO's focus on known methods for potentially isolating the claimed DNA molecules is misplaced because the claims at issue define compounds, not methods." *In re Deuel*, 34 USPQ2d at 1215. The CAFC further stated that "[a] general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search." *Id.* The same reasoning applies equally to the improved human anti-hTNFα antibodies of the invention that have specifically-defined structural features. Thus, for the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness for at least claims 9-20. If the Examiner insists on maintaining this rejection, Applicants respectfully request that the Examiner particularly point out where in the prior art there is a specific suggestion or

motivation to make the specific molecular modifications to the antibodies of Griffiths *et al.* that would be necessary to achieve the antibodies of claims 9-20.

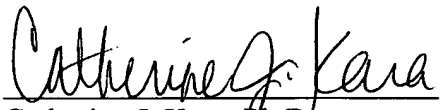
For all of the foregoing reasons, the antibodies and compositions of pending claims 1-23 and 44 are nonobvious over Griffiths *et al.* (EMBO J.) in view of Lewis *et al.* (WO 95/23813) or Lewis *et al.* (J. Cell. Biochem.). Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection under 35 U.S.C. §103.

SUMMARY

In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested.

If a telephone conversation with Applicants' Agent would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Agent at (617) 227-7400.

Respectfully submitted,



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Dated: February 5, 1998

APPENDIX A

1. An isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-7} M or less.

2. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which dissociates from human TNFα with a K_{off} rate constant of 5×10^{-4} s^{-1} or less, .

3. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which dissociates from human TNFα with a K_{off} rate constant of 1×10^{-4} s^{-1} or less.

4. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-8} M or less.

5. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-9} M or less.

6. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an IC_{50} of 1×10^{-10} M or less.

7. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which is a recombinant antibody, or antigen-binding portion thereof.

8. The isolated human antibody, or antigen-binding portion thereof, of claim 1, which inhibits human TNFα-induced expression of ELAM-1 on human umbilical vein endothelial cells.

9. An isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

a) dissociates from human TNFα with a K_{off} rate constant of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

10. The isolated human antibody of claim 9, or an antigen-binding portion thereof, which dissociates from human TNFα with a K_{off} rate constant of 5×10^{-4} s^{-1} or less.

11. The isolated human antibody of claim 9, or an antigen-binding portion thereof, which dissociates from human TNFα with a K_{off} rate constant of 1×10^{-4} s^{-1} or less.

12. An isolated human antibody, or an antigen-binding portion thereof, with a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, and with a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11.

13. The isolated human antibody, or an antigen-binding portion thereof, of claim 12, wherein the LCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5 and the HCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6.

14. The isolated human antibody, or an antigen-binding portion thereof, of claim 13, wherein the LCVR further has CDR1 domain comprising the amino acid

sequence of SEQ ID NO: 7 and the HCVR has a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

15. An isolated human antibody, or an antigen binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

16. The isolated human antibody of claim 15, which has an IgG1 heavy chain constant region.

17. The isolated human antibody of claim 15, which has an IgG4 heavy chain constant region.

18. The isolated human antibody of claim 15, which is a Fab fragment.

19. The isolated human antibody of claim 15, which is a single chain Fv fragment.

20. An isolated human antibody, or an antigen-binding portions thereof, with a light chain variable region (LCVR) having a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26 or with a heavy chain variable region (HCVR) having a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34.

21. An isolated human antibody, or antigen-binding portion thereof, that neutralizes the activity of human TNFα, chimpanzee TNFα and at least one additional primate TNFα selected from the group consisting of baboon TNFα, marmoset TNFα, cynomolgus TNFα and rhesus TNFα.

22. The isolated human antibody, or an antigen-binding portion thereof, of claim 21, which also neutralizes the activity of mouse TNFα.

23. The isolated human antibody, or an antigen-binding portion thereof, of claim 21, which also neutralizes the activity of pig TNFα.

44. A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any one of claims 1-23, and a pharmaceutically acceptable carrier.

65. The pharmaceutical composition of claim 44, which further comprises at least one additional therapeutic agent.

APPENDIX B

Light Chain CDR3

	1	2	3	4	5	6	7	8	9
αTNF-A1	Q	Q	T	T	S	F	P	L	T
αTNF-E1	Q	Q	A	N	S	F	P	L	T
αTNF-E7	Q	Q	A	N	S	L	P	P	T
αTNF-H9G1	Q	S	Y	D	S	R	L	I	R	V
SEQ ID NO: 3	Q	**R**	Y	N	**R**	**A**	P	**Y**	T

Heavy Chain CDR3

	1	2	3	4	5	6	7	8	9	10	11	12
αTNF-A1	E	D	H	V	I	T	T	G	R	Y	H	Y	Y	M	D	V
αTNF-E1	E	D	Y	V	I	T	S	G	F	Y	Y	Y	H	M	D	V
αTNF-E7	G	P	L	R	G	Y	D	Y	Y	Y	Y	M	D	V		
αTNF-H9G1	S	G	D	L	Y	S	G	Y	E	D						
SEQ ID NO: 4	**V**	**S**	Y	L	**S**	T	**A**	**S**	**S**	**L**	**D**	Y				